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Assessment of Pre-operative Vaginal Preparation for Laparoscopic Hysterectomy

Michelle Marinone, MD, Jonathan Serino, BS, Stephanie Stroever, PhD, MPH, Nicole Brzozowski, MD, Andrea Kliss, MA, David Doo, MD, Linus Chuang, MD

ABSTRACT

Objective: Determine the difference in microbial growth from the vagina and uterine manipulator among patients undergoing laparoscopic hysterectomy after randomization to one of three vaginal preparation solutions (10% Povidone-iodine, 2% Chlorhexidine, or 4% Chlorhexidine).

Method: This was a prospective randomized controlled trial in an academic community hospital. Patients were ≥ 18 years old and scheduled for laparoscopic hysterectomy for benign and malignant indications.

Results: Fifty patients were identified and randomized into each arm. Prior to surgery, the surgical team prepared the vaginal field using 10% Povidone-iodine, 2% Chlorhexidine, or 4% Chlorhexidine, according to group assignment. Cultures were collected from the vagina after initial preparation, prior to the colpotomy, and on surfaces of the uterine manipulator. Bacterial count from the baseline vaginal fornix/cervical canal cultures did not differ significantly among the three groups. There was a difference in bacterial count among the second cervical canal/vaginal fornix cultures ($p < 0.01$), with the Povidone-iodine arm demonstrating the highest level of growth of cultures (93.8%), followed by 2% Chlorhexidine (47.4%), and 4% Chlorhexidine (20%). There was no difference in growth on the uterine manipulator handle and no difference in vaginal itching or burning was found across the three arms postoperatively.

Conclusion: Bacterial growth prior to colpotomy was the lowest with 4% Chlorhexidine followed by 2% Chlorhexidine, the Povidone-iodine group exhibited the highest bacterial growth. There was no difference in moderate to severe vaginal itching or burning. This showed that 4% Chlorhexidine is superior in reducing bacterial growth when used in laparoscopic hysterectomy.

Key Words: Bacterial growth, Chlorhexidine, Hysterectomy, Laparoscopy, Povidone-iodine.

INTRODUCTION

Laparoscopic hysterectomy is a "clean-contaminated" procedure. Vaginal bacteria can ascend into the operative field, increasing the risk for surgical site infection (SSI).[1] Pre-operative antibiotics and two field antisepsis are major defenses against SSI.[2] Two percent chlorhexidine gluconate (CHG) skin prep has been shown to reduce SSI in clean-contaminated surgeries vs povidone-iodine (PI).[3] PI is the only solution currently FDA-approved for vaginal preparation; however, CHG with low isopropyl alcohol content is commonly used off-label.[2] CHG is available in 2% and 4% solutions. Many providers recommend the routine use of 4% CHG due to prior studies demonstrating decreased vaginal bacterial colony counts after cleansing with 4% CHG vs PI.[4]

The manufacturer's label for CHG discourages its use on genitals due to concerns for allergies and irritation. Hence, some operating room staff remain hesitant to use CHG.[4] Several studies exist utilizing dilute CHG vaginal lavage in obstetric populations with no reported significant adverse effects.[5–7] These results cannot necessarily be

Green Valley OB/GYN, Greensboro, North Carolina, USA. (Dr. Marinone)

USF Health Morsani College of Medicine, Tampa, Fl, USA. (Mr. Serino)

Department of Medical Education and Clinical Research Institute, Texas Tech University Health Sciences Center, Lubbock, TX, USA. (Dr. Stroever)

Departments of Obstetrics, Gynecology, and Reproductive Biology, Danbury Hospital of Nuvance Health, Danbury, CT, USA. (Drs. Brzozowski, Doo, and Chuang)

Performance Improvement- Quality, Danbury Hospital of Nuvance Health, Danbury, CT, USA. (Ms. Kliss)

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Address correspondence to: Dr. Linus Chuang, MD, 24 Hospital Avenue, Danbury, CT, 06810, Telephone: 203-240-3486, E-mail: Linus.Chuang@nuvancehealth.org.

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extrapolated to gynecologic surgery. An RCT comparing the tolerability of vaginal 4% CHG vs PI in hysteroscopy showed that use of CHG was associated with worse postop vaginal symptoms.[8] In contrast, 2% CHG when compared to PI has not been associated with increased postop vaginal irritation.[9]

Our study's primary objective was to determine a difference in microbial growth at the vaginal field in laparoscopic hysterectomy patients after randomization to PI, 2% CHG, or 4% CHG. Our secondary objective was to identify any difference in postoperative vaginal discomfort.

METHODS

Trial Design

We conducted a single-blind, randomized controlled trial with a parallel design and an allocation ratio of 1:1:1 to compare vaginal site preparation with 2% CHG, 4% CHG, and 10% PI in patients undergoing elective laparoscopic hysterectomy (including robot-assisted). This study was reviewed and approved by the Institutional Review Board.

Participants

The trial was conducted from February 1, 2020 to March 31, 2021. Study personnel screened patients undergoing elective laparoscopic hysterectomy where the uterine manipulator is used (including robot-assisted) and consented interested candidates during the pre-operative visit.

We included females scheduled for laparoscopic hysterectomy for both benign and malignant indications if they were $\geq$ 18 years old and spoke English or Spanish. We excluded patients if they had a history of allergy to chlorhexidine, alcohol, or iodine. We also excluded patients with immunodeficiency or known pre-operative infection. Lastly, we excluded participants from the analysis if their surgery was converted to open mid-procedure.

Interventions

Prior to initiation of surgery, and after receiving the prophylactic antibiotics, the surgical team prepared the vaginal field using 10% PI, 2% CHG, or 4% CHG, according to the a priori group assignment. A sponge was used to scrub the perineum, top third of the thighs, vulva, and then the vaginal interior up to the cervix. The sponge was then discarded after swabbing the anus. This scrub was repeated two more times and allowed to dry according to the manufacturers' guidelines.

Following sterile preparation, a member of the surgical team collected the first culture swab of the vagina. Then, directly prior to the colpotomy, a second culture swab of the vagina was collected. The vaginal swabs were swept throughout the length of the vagina with focused attention to swabbing all vaginal surfaces.[10] Thorough swabs were collected of all vaginal surfaces in replacement of the cervical canal. Prior to the colpotomy, a third culture swab premoistened with sterile saline was run slowly over all available surfaces of the uterine manipulator. During the surgery, the surgeons changed gloves after any direct contact with the manipulator or vaginal field. The surgery was otherwise completed according to standards of care.

All swabs were handed to study staff who closed, labeled, and sealed them in a specimen bag. This bag was sent to the microbiology laboratory and was plated for aerobic and anaerobic cultures. This process proceeded according to the hospital's microbiology laboratory policies for wound cultures. Laboratory staff plated all specimens semiquantitatively on sheep blood, MacConkey, and chocolate agar. Laboratory staff then inoculated thioglycollate broth and all media were incubated at 37 °C under appropriate oxygen requirements. Cultures with no growth were finalized after 48 hours of incubation, and cultures with growth reflexed as appropriate for identification and/or antibiotic sensitivity testing. Thioglycollate broth cultures were held for a total of seven days if no growth after 48 hours.

Outcomes

The primary outcome of this study was the presence or absence of bacterial growth on aerobic and anaerobic wound culture, as well as in thioglycollate broth on any of the three culture swabs taken throughout the surgery. Positive bacterial growth was defined as rare or greater microbial growth on a semiquantitative scale or any growth in the thioglycollate broth. Very rare Gram-positive cocci were considered environmental contaminants and were ignored. The secondary outcome was patient-reported vaginal itching and burning (scale from 0–5 with 0 being "no itching/burning" and 5 being "severe itching/burning") collected on postoperative day one by blinded study personnel. The finding of vaginal burning is underpowered to draw a definitive conclusion for the secondary outcome.

We also collected data on participant demographics and baseline clinical characteristics including age, race/ethnicity, body mass index (BMI), past medical history, and smoking history (ever or never). We also collected surgery date, time, and duration, procedure(s) performed, surgery method (laparoscopic or robotic), pre/postoperative diagnoses, estimated blood loss, and intraoperative complications. Lastly, we collected the length of hospital stay and 30-day postoperative complications, including SSI as defined according to the National Healthcare Safety Network definitions for gynecologic procedures.[11]

Sample Size

We estimated the sample size using baseline and comparison proportions of 0.3 and 0.6 at 85% power, respectively. The result was a conservative estimate of 144 patients, 48 per group. Interim analyses after enrollment of 43 patients resulted in statistically significant differences across groups. Thus, we chose to halt enrollment and report the results of those enrolled to date. The sample size was limited due to only two primary surgeons involved in the single institution.

Randomization

Participants were assigned to groups via a computer-generated randomization schedule in blocks of 12.

Blinding

The subjects were blind to their randomization group, and postoperative vaginal itching and burning were collected via telephone by blinded study personnel.

Statistical Methods

All statistical analyses were completed with StataSE version 16 (StataCorps, LLC, College Station, Texas), and missing data were handled using the default, listwise deletion. We calculated descriptive statistics using mean with standard deviation for continuous variables, median with interquartile range for rank, and number with percentage for categorical. Differences in sample characteristics across the three groups were assessed using one-way analysis of variance for normally distributed continuous variables or the Kruskal-Wallis rank test for those that were not normally distributed. Normality was confirmed using the Shapiro-Wilk W test. We used χ^2 for categorical variables with cell counts ≥ 5 or Fisher's exact test for those with < 5.

To test the null hypothesis that there was no difference in microbial growth across the three presurgical preparations (two-tailed alternative hypothesis), we used the Fisher's exact test with $\alpha = 0.05$ established a priori. We assessed growth on each swab independently. To test the null hypothesis that there was no difference in vaginal itching or burning on postoperative day one across groups (two-tailed alternative hypothesis), we also used Fisher's exact test. Itching and burning were assessed independently as well with $\alpha = 0.05$.

Post-Hoc Analyses

There was a statistically significant difference in the proportion of obese patients in each preparation group. Thus, we stratified our analyses by obesity status to elucidate potential confounding in our results. We repeated all analyses described above by subgroup.

RESULTS

A total of 50 women were enrolled in the study and randomized into each arm. Baseline characteristics were similar across each arm, with the exception of obesity. There were significantly fewer patients with BMI > 30 in the 2% CHG (n = 6, 31.58%) compared to the other two arms (PI: n = 10, 62.5%; 4% CHG: n = 12, 80%) (**Table 1**). There were no difference in the parameters among the three study groups.

Surgical characteristics were similar across each arm as well. Of the surgeries performed, 29 were laparoscopic hysterectomies and 21 were robot-assisted laparoscopic hysterectomies. Intraoperative and postoperative complication rates were very low. There was only one case of SSI, which presented in the postoperative period as vaginal cuff cellulitis in a patient in the PI group (**Table 2**). The cellulitis rate of 2% is consistent with the 1.6% rate documented of laparoscopic hysterectomies.[12]

Bacterial growth from the baseline vaginal fornix cervical canal cultures did not differ significantly among the three groups (**Table 2**). There was a difference in bacterial growth among the second vaginal fornix/cervical canal cultures ($p < 0.01$), with the PI arm demonstrating the highest level of growth (in 93.8% of cultures), followed by 2% CHG (in 47.4% of cultures), and 4% CHG (in 20% of cultures). There was no difference in growth on the uterine manipulator handle. Additionally, no difference in moderate to severe vaginal itching or burning was found across the three arms on postoperative day one ($p = 0.78$ and 0.29, respectively).

Table 1.
Descriptive Statistics for Prospective, Randomized Study of Three Sterile Preparation Chemicals for Vaginal Field Prior to Laparoscopic/Robotic Hysterectomy from 2020–2021

Variable	Betadine	2% CHG	4% CHG	*p*-Value[a]
Total Sample	16	19	15	
Age [mean (SD)]	61.4 (13.5)	60.2 (13.1)	55.7 (14.6)	0.472
Body mass index [mean (SD)]	33.62 (8.88)	29.83 (8.32)	34.57 (6.39)	0.190
Race/Ethnicity [n (%)]				0.077
Black	0 (0.00)	0 (0.00)	2 (13.33)	
White	13 (81.25)	11 (57.89)	8 (53.33)	
Asian	0 (0.00)	1 (5.26)	0 (0.00)	
Hispanic or Latino	2 (12.50)	6 (31.58)	1 (6.67)	
Unknown/Not Reported	1 (6.25)	1 (5.26)	4 (26.67)	
Diabetes [n (%)]	3 (18.75)	1 (5.26)	3 (20.00)	0.396
Hypertension [n (%)]	8 (50.00)	7 (36.84)	7 (46.67)	0.769
Asthma [n (%)]	1 (6.25)	1 (5.26)	0 (0.00)	1.000
COPD [n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	n/a
Obesity [n (%)]	10 (62.50)	6 (31.58)	12 (80.00)	0.016
Depression [n (%)]	1 (6.25)	2 (10.53)	3 (20.00)	0.562
Anxiety [n (%)]	0 (0.00)	4 (21.05)	3 (20.00)	0.147
Alcohol Abuse [n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	n/a
Drug Abuse [n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	n/a
Chronic Pain Disorder [n (%)]	2 (12.50)	1 (5.26)	1 (6.67)	0.822
Smoking Status (ever) [n (%)]	11 (68.75)	6 (31.58)	7 (46.67)	0.090
Surgery Method [n (%)]				0.64
Laparoscopic	8 (50.0)	11 (57.9)	10 (66.7)	
Robotic	8 (50.0)	8 (42.1)	5 (33.3)	
Blood products required [Median (IQR)]	50 (87.50)	100 (50.00)	50 (75.00)	0.683
Intraoperative Bowel Injury	0 (0.00)	0 (0.00)	0 (0.00)	n/a
Intraoperative Vascular Injury	0 (0.00)	0 (0.00)	0 (0.00)	n/a
Other Intraoperative Complication[b]	0 (0.00)	0 (0.00)	1 (6.67)	0.30
Surgery Duration [n (%)]				0.470
≤120 minutes	4 (25.00)	6 (31.68)	3 (20.00)	
121–150 minutes	3 (18.75)	3 (15.79)	7 (46.67)	
151–180 minutes	6 (37.50)	5 (26.32)	3 (20.00)	
>180 minutes	3 (18.75)	5 (26.32)	2 (13.33)	
Surgical Site Infection [n (%)]	1 (6.25)	0 (0.00)	0 (0.00)	0.620
Wound Dehiscence [n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	n/a
Hematoma [n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	n/a
Other Postop Complication [n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	n/a

Table 1. Continued

Variable	Betadine	2% CHG	4% CHG	*p*-Value[a]
Inpatient Stay [n (%)]				0.310
1 day	4 (25.00)	4 (21.05)	5 (33.33)	
2 days	9 (56.25)	10 (52.63)	10 (66.67)	
3 days	3 (18.75)	5 (26.32)	0 (0.00)	

[a]Crude analysis of group differences; ANOVA or Kruksal-Wallis rank test for continuous variables, Fisher's exact or χ^2 for categorical variables.
[b]Bladder injury.
Abbreviations: CHG, chlorhexidine gluconate; COPD, chronic obstructive pulmonary disease; SD, standard deviation; IQR, interquartile range.

A posthoc data analysis divided the sample into obese (BMI ≥ 30) and nonobese (BMI < 30) groups. In this analysis, the decrease in bacterial growth with CHG prior to colpotomy was only appreciated in the obese group ($p < 0.01$) and was not found in the nonobese group ($p = 0.09$).

DISCUSSION

Prevention of surgical site infection is an important tenet of perioperative care. SSI safety bundles have emerged as an effective tool to improve outcomes and reduce morbidity.[2] In our institution at the time of IRB

Table 2.
Inferential Statistics for Prospective, Randomized Study of Three Sterile Preparation Chemicals for Vaginal Field Prior to Laparoscopic/Robotic Hysterectomy from 2020–2021

Variable	Betadine	2% CHG	4% CHG	*p*-Value[a]
Total Subjects	16	19	15	
All subjects				
Bacterial growth at baseline vaginal fornix/cervical canal [n (%)]	1 (6.3)	1 (5.3)	0 (0.0)	1.00
Bacterial growth at second vaginal fornix/cervical canal [n (%)]	15 (93.8)	9 (47.4)	3 (20.0)	**<0.01**
Bacterial growth on uterine manipulator [n (%)]	1 (6.3)	4 (21.1)	1 (6.7)	0.35
Moderate to severe vaginal itching [n (%)]	2 (12.5)	2 (10.5)	3 (20.0)	0.78
Moderate to severe vaginal burning [n (%)][b]	4 (25.0)	2 (10.5)	5 (33.3)	0.29
Body mass index < 30				
Bacterial growth at baseline vaginal fornix/cervical canal [n (%)]	0 (0.0)	1 (7.7)	0 (0.0)	1.00
Bacterial growth at second vaginal fornix/cervical canal [n (%)]	6 (100.0)	7 (53.9)	1 (33.3)	0.09
Bacterial growth on uterine manipulator [n (%)]	0 (0.0)	3 (23.1)	0 (0.0)	0.70
Moderate to severe vaginal itching [n (%)]	0 (0.0)	2 (15.4)	1 (33.3)	0.51
Moderate to severe vaginal burning [n (%)]	1 (16.7)	1 (7.7)	2 (66.7)	0.08
Body mass index ≥ 30				
Bacterial growth at baseline vaginal fornix/cervical canal [n (%)]	1 (10.0)	0 (0.0)	0 (0.0)	0.57
Bacterial growth at second vaginal fornix/cervical canal [n (%)]	9 (90.0)	2 (33.3)	2 (16.7)	**<0.01**
Bacterial growth on uterine manipulator [n (%)]	1 (10.0)	1 (16.7)	1 (8.3)	1.00
Moderate to severe vaginal itching [n (%)]	2 (20.0)	0 (0.0)	2 (16.7)	0.65
Moderate to severe vaginal burning [n (%)]	3 (30.0)	1 (16.7)	3 (25.0)	1.00

[a]Fisher's exact.
[b]The finding of Vaginal burning is underpowered to draw a definitive conclusion for the secondary outcome.
Abbreviations: CHG, chlorhexidine gluconate.

approval of our study in 2019, 2% CHG solutions were routinely used for vaginal preparation in an effort to minimize bacterial load as well as patient irritation. As a result of our study, we have changed our institutional practice to the routine use of 4% CHG. This is in line with the American Association of Gynecologic Laparoscopists 2020 task force consensus that 4% CHG should be used for vaginal preparation as part of an Enhanced Recovery After Surgery protocol.[13]

To our knowledge, our study is the first to perform a prospective three-way comparison among the three vaginal prep solutions, which includes both commercially available concentrations of CHG. Our study further bolsters the support for using CHG for routine pre-operative vaginal preparation, while adding the superiority of 4% CHG compared to 2% CHG. This study also demonstrates similar patient tolerability with all three solutions. While severe adverse reactions such as vaginal desquamation have been reported with 4% CHG, we feel these are sufficiently rare events that should not preclude its routine use.[14]

A "cleaner" surgical site should theoretically lead to reduced SSIs. Indeed, the only SSI observed in our study occurred in the PI group, which also had the highest frequency of bacterial growth. It is not surprising that the more dilute 2% CHG solution was less effective at preventing bacterial growth prior to colpotomy than the 4% CHG solution. However, our secondary analysis demonstrated that the decrease in bacterial growth prior to colpotomy observed with CHG as compared to PI was driven mostly by the obese participants. This could be due to alterations in the vaginal microbe burden in obese women. Perhaps 4% CHG is only superior in women with a certain profile of bacterial flora. Further studies are needed to examine this relationship.

Interestingly, a 2021 retrospective analysis published after the completion of our study found lower rates of infections and postoperative emergency department visits when using PI rather than CHG. PI is more effective against gram negative bacteria and anaerobes, which are the leading pathogens in post-hysterectomy infections. The authors hypothesized that improved bactericidal activity of PI against these specific microbes may be more important in reducing postoperative morbidity than the lower bacterial counts observed with CHG.[15] It remains to be seen if this 2021 study marks the beginning of a pendulum swing back towards favoring the routine use of PI.

Limitations of our study include a small sample size due to the involvement of only two primary surgeons at a single institution. Bacterial growth was used as a surrogate marker in our study for SSI. There have been recent concerns raised in the literature that development of subsequent SSI is likely more complex than which solution renders a "cleaner" operative field. Future research efforts should be prospective, collaborative to achieve a large sample size, and focus on the patient important outcomes of surgical site infection and patient tolerability to determine which vaginal antiseptic is truly superior. The American College of Obstetricians and Gynecologists has not updated its infection prevention recommendations since 2018, which maintains that both 4% CHG and PI are acceptable routine vaginal prep solutions based on surgeon preference.[2]

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